

Attorney Docket No. P63142US1  
Application No. 09/806,509

**Amendments to the claims:**

This listing of claims replaces all prior versions, and listings, of claims in the application.

**Listing of claims:**

Claims 1-22 (cancelled).

Claim 37 (new): A method for diagnosing or prognosing Alzheimer's disease in a subject, or determining whether a subject is at increased risk of developing Alzheimer's disease, comprising:

- measuring at least one of a level or biological activity of a transcription product and/or a translation product of (i) the cystatin C gene or (ii) a polymorphic variant of the cystatin C gene in at least one sample of cerebrospinal fluid from the subject; and
- comparing the at least one measured level or biological activity with a corresponding control from a non-Alzheimer's-diseased individual;

whereby, when the measured level or biological activity is elevated relative to the corresponding control, a diagnosis, or prognosis, or increased risk of Alzheimer's disease in the subject is indicated.

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Claim 38 (new): A method of monitoring the progression of Alzheimer's disease in a subject, comprising:

- measuring at least one of a level or biological activity of a transcription product and/or a translation product of (i) the cystatin C gene or (ii) a polymorphic variant of the cystatin C gene in cerebrospinal fluid from the subject; and
- comparing the at least one measured level or biological activity with a corresponding control from a non-Alzheimer's-diseased individual;

thereby monitoring the progression of Alzheimer's disease in the subject.

Claim 39 (new): A method of evaluating a treatment for Alzheimer's disease, comprising:

- measuring at least one of a level or biological activity of a transcription product and/or a translation product of (i) the cystatin C gene or (ii) a polymorphic variant of the cystatin C gene in cerebrospinal fluid from the subject; and
- comparing the at least one measured level or biological activity with a corresponding control from a non-Alzheimer's-diseased individual;

thereby evaluating the treatment for Alzheimer's disease.

Claim 40 (new): The method according to claim 37, wherein the translation product is cystatin C in its monomer form.

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Claim 41 (new): The method according to claim 37, wherein the translation product and/or the transcription product is detected using an immunoassay, an enzyme activity assay and/or a binding assay.

Claim 42 (new): The method according to claim 37, wherein the reference value is that of a level, or an activity, or both the level and the activity, of a transcription product and/or a translation product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene in a sample from a subject not suffering from the Alzheimer's disease.

Claim 43 (new): The method according to claim 37, wherein the at least one sample of cerebrospinal fluid is a series of samples of cerebrospinal fluid taken from the subject over a period of time.

Claim 44 (new): The method according to claim 43, wherein the subject receives a treatment for Alzheimer's disease prior to one or more sample gatherings.

Claim 45 (new): The method of claim 44, wherein the at least one level or biological activity in the samples is determined before and after the treatment of the subject.

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Claim 46 (new): A method of diagnosing or prognosing Alzheimer's disease in a subject, or determining whether a subject is at increased risk of developing Alzheimer's disease comprising:

- determining a presence or absence of a polymorphism in a cystatin C gene in a sample from the subject,
- thereby diagnosing or prognosing Alzheimer's disease in the subject, or determining whether the subject is at increased risk of developing Alzheimer's disease.

Claim 47 (new): The method of claim 46, wherein a presence of a polymorphism is determined in leucin 68 codon of the cystatin C gene, leading to a loss of Alu I restriction site, indicating no increased risk of Alzheimer's disease in the subject.

Claim 48 (new): The method of claim 46, wherein the presence of at least one B allele is determined.

Claim 49 (new): The method of claim 48, wherein presence of the at least one B allele indicates the subject is at increased risk of developing Alzheimer's disease or indicates a diagnosis or prognosis of Alzheimer's disease.

Claim 50 (new): The method of claim 49, wherein the at least one B allele is of the B/B genotype.

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Claim 51 (new): The method of claim 46, further comprising:

- determining a level, or an activity, or both the level and the activity, of a transcription product and/or a translation product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene in a sample from the subject; and
- comparing the level, or the activity, or both the level and the activity, of the transcription product and/or the translation product to a reference value representing a known disease or health status.

Claim 52 (new): A method of using a kit for the diagnosis, or prognosis, or determination of increased risk of developing Alzheimer's disease, or monitoring a progression, or monitoring success or failure of a therapeutic treatment of Alzheimer's disease in a subject, the method comprising:

- measuring at least one of a level or biological activity of a transcription product and/or a translation product of (i) the cystatin C gene or (ii) a polymorphic variant of the cystatin C gene in at least one sample of cerebrospinal fluid from the subject; and
- comparing the at least one measured level or biological activity with a corresponding control from a non-Alzheimer's-diseased individual;

whereby, when the measured level or biological activity is elevated relative to the corresponding control, a diagnosis, or prognosis, or increased risk of Alzheimer's disease in the subject is indicated, wherein the kit comprises

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- a) at least one reagent selected from the group consisting of
  - reagents that selectively detect a transcription product of (i) the cystatin C gene or (ii) a polymorphic variant of the cystatin C gene,
  - reagents that selectively detect a translation product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene, and
  - reagents that selectively detect the presence or absence of a polymorphism in the cystatin C gene; and
- b) instructions for performing the method.

Claim 53 (new): The method according to claim 52, wherein the kit further comprises a reagent that assesses function or dysfunction of the subject's kidneys.

Claim 54 (new): The method according to claim 52, wherein the translation product is cystatin C in its monomer form.

Claim 55 (new): The method according to claim 52 for use in monitoring a progression of Alzheimer's disease in a subject.

Claim 56 (new): The method according to claim 52 for use in monitoring success or failure of a therapeutic treatment of the subject.

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Claim 23 (withdrawn): A kit for the diagnosis or prognosis, or determination of increased risk of developing Alzheimer's disease in a subject, the kit comprising:

- (a) reagents that selectively detect the presence or absence of a polymorphism in a cystatin C gene; and
- (b) instructions for diagnosing, or prognosing, or determining increased risk of developing Alzheimer's disease in a subject by
  - determining the presence or absence of a polymorphism in a cystatin C gene; and
  - diagnosing, or prognosing, or determining whether the subject is at increased risk of developing Alzheimer's disease;

wherein the presence of at least one B allele, in particular the presence of the B/B genotype, indicates a diagnosis, or prognosis, or an increased risk of developing Alzheimer's disease

Claim 24 (withdrawn): The kit according to claim 23, further comprising

- (a) reagents that selectively detect a transcription product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene,  
reagents that selectively detect a translation product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene, and
- (b) instructions for diagnosing, or prognosing, or determining increased risk of developing Alzheimer's disease in a subject by

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- detecting a level, or an activity, or both the level and the activity, of the transcription product and/or the translation product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene, in a sample from the subject; and
- diagnosing, or prognosing, or determining whether the subject is at increased risk of developing Alzheimer's disease, wherein a varied level, or activity, or both the level and the activity, of the transcription product compared to a reference value representing a known health status; or an increase of a level or a varied activity of the translation product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene relative to a reference value representing a known health status; or a level, or activity, or both the level and the activity, of the transcription product and/or the translation product similar or equal to a reference value representing a known disease status indicates a diagnosis, or prognosis, or increased risk of developing Alzheimer's disease.

Claim 25 (withdrawn): The kit according to claim 23, wherein a presence of a polymorphism in leucin 68 codon of a human cystatin C gene leading to a loss of Alu I restriction site does not indicate diagnosis or prognosis of Alzheimer's disease in the subject.

Claim 26 (withdrawn): The kit according to claim 23, further comprising reagents to assess a function or dysfunction of the subject's kidneys.



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Claim 27 (withdrawn): The kit according to claim 23, wherein the translation product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene is determined in its monomer form.

Claim 28 (withdrawn): A method of treating or preventing Alzheimer's disease in a subject comprising administering to the subject in a therapeutically effective amount an agent or agents which directly or indirectly affect an activity, or level, or both the activity and level, of

a cystatin C gene or a polymorphic variant of a cystatin C gene, and/or

a transcription product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene, and/or

a translation product of (i) a cystatin C gene or (ii) a polymorphic variant of a cystatin C gene.

Claim 29 (withdrawn): The method according to claim 28, wherein the agents are cathepsin derivatives or cystatin C analogs.

Claim 30 (withdrawn): The method according to claim 28, wherein per se known methods of gene therapy and/or antisense nucleic acid technology are applied to administer the agent or agents.

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Claim 31 (withdrawn): The method according to claim 28 comprising grafting donor cells into the central nervous system, preferably the brain, of the subject, the subject or donor cells preferably treated so as to minimize or reduce graft rejection, wherein the donor cells are genetically modified by insertion of at least one transgene encoding the agent or agents.

Claim 32 (withdrawn): An agent which directly or indirectly affects an activity, or level, or both the activity and level, of at least one substance which is selected from the group consisting of a cystatin C gene, a polymorphic variant of a cystatin C gene, a transcription product of a cystatin C gene, a transcription product of a polymorphic variant of a cystatin C gene, a translation product of a cystatin C gene and a translation product of a polymorphic variant of a cystatin C gene.

Claim 33 (withdrawn): A medicament comprising an agent according to claim 32.

Claim 34 (withdrawn): An agent which directly or indirectly affects an activity, or level, or both the activity and level, of at least one substance which is selected from the group consisting of a cystatin C gene, a polymorphic variant of a cystatin C gene, a transcription product of a cystatin C gene, a transcription product of a polymorphic variant of a cystatin C gene, a translation product of a cystatin C gene and a translation product of a polymorphic variant of a cystatin C gene for treating or preventing a disease.

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Claim 35 (withdrawn): Use of an agent which directly or indirectly affects an activity, or level, or both the activity and level, of at least one substance which is selected from the group consisting of a cystatin C gene, a polymorphic variant of a cystatin C gene, a transcription product of a cystatin C gene, a transcription product of a polymorphic variant of a cystatin C gene, a translation product of a cystatin C gene and a translation product of a polymorphic variant of a cystatin C gene for a preparation of a medicament for treating or preventing a neurodegenerative disease, in particular Alzheimer's disease.

Claim 36 (withdrawn): A method for identifying an agent that directly or indirectly affects an activity, or level, or both the activity and level, of at least one substance which is selected from the group consisting of a cystatin C gene, a polymorphic variant of a cystatin C gene, a transcription product of a cystatin C gene, a transcription product of a polymorphic variant of a cystatin C gene, a translation product of a cystatin C gene and a translation product of a polymorphic variant of a cystatin C gene, comprising the steps of:

- (a) providing a sample comprising at least one substance which is selected from the group consisting of a cystatin C gene, a polymorphic variant of a cystatin C gene, a transcription product of a cystatin C gene, a transcription product of a polymorphic variant of a cystatin C gene, a translation product of a cystatin C gene and a translation product of a polymorphic variant of a cystatin C gene;
- (b) contacting the sample with at least one agent;

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- (c) comparing an activity, or level, or both the activity and level, of at least one of the substances before and after the contacting.